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REMARKS

Upon entry of the above amendment, claims 16-20, 24-30, and 33-45 will be pending, claims 31 and 32 having been newly canceled. Applicants have amended claims 18 and 30. Support for the amendment to claim 30 can be found at page 27 bridging to page 28. Support for the amendment to claim 18 can be found throughout the specification and claims as filed. No new matter has been added.

Rejections Under 35 USC § 112, second paragraph

Claims 18-20 and 24-45 were rejected under 35 USC § 112, second paragraph, as allegedly indefinite. The Office action, at page 3, states that:

> [O]n page 36 of the specification, applicant defines "organ" in opposition to art accepted definition to include tissues and cells, even a single cell. Thus, there is confusion regarding these terms. Although applicant may be their own lexicographer, there is no need to complicate matters by confusing the well-known distinctions in science and medicine that exist between organs, tissues and cells.

Applicants have amended claim 18 to recite a "whole organ." This amendment is supported implicitly and/or inherently by the specification and claims as filed, e.g., in the specification at page 36, lines 16-20, where several whole organs (e.g., kidney, liver, heart, and pancreas) are listed. The discussion of "portions of an organ" at page 36 implies that the "organ" from which the "portions" are derived is a whole organ. Applicants submit that the meaning of the term "whole organ" in claim 18 is clear and request reconsideration and withdrawal of the rejection for alleged indefiniteness.[1]

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[1] Applicants do not concede that the specific definitions of "organ," "tissue," and "cell" provided at page 3 of the Office action necessarily represent the meanings the terms would have had to a person of ordinary skill in the art at the time of the invention.

Rejections Under 35 USC § 112, first paragraph

Claims 30-36 were rejected under 35 USC § 112, first paragraph, as allegedly containing new matter.

The Office Action states, at page 2, that the limitation concerning the timing of administration of "nitric oxide and the second treatment" in claims 30-32 is not supported by the specification as filed. Without conceding the point, and solely to further prosecution, applicants have canceled claims 31-32 and amended claim 30 to recite that the second treatment is CO and is administered to the recipient within 20 days after (b). This limitation finds support in the specification as filed, e.g., at page 28, lines 9-13.

The Office Action also states that there is no support in the specification as filed for the recitation of "live donor" in claim 35 and "brain-dead donor" in claim 36. Applicants traverse.

To comply with the written description requirement, each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure. See MPEP § 2613. The recitation of a "brain-dead donor" is expressly supported in the specification at page 34, line 5. The recitation of a "live donor" is implicitly and/or inherently supported by the disclosure. At several places in the specification, there is description of administering gaseous compositions that include, e.g., NO and CO, by inhalation. For example, at page 12, the specification lists face masks, tents and portable inhalers as means of administration, all of which require spontaneous ventilation, and thus implicitly require that the patient be alive. Further, at page 23, lines 26-27, the specification indicates that a liquid composition, e.g., may be administered to a "living animal." Because the concept of a "live donor" is inherently and/or implicitly supported by the specification, it does not constitute new matter.

The Office Action further states at page 2, that the recitation of "upon determination that the transplanted organ is undergoing or about to undergo chronic rejection," in claim 33 is not supported by the disclosure. Applicants submit that the recitation can be reasonably determined from the specification as filed. Chronic rejection is described in the specification at page 36, lines 9-14.[2] Further, the specification states at page 10, lines 27-29, that "a patient can be

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[2] Applicants note that acute rejection is also described in the specification at this location.

diagnosed by a physician . . . as suffering from or at risk for a condition described herein by any method known in the art." Therefore, the concept of determining that the transplanted organ is undergoing or about to undergo chronic rejection is inherently and/or implicitly disclosed in the specification as filed and does not constitute new matter.

For at least the foregoing reasons, applicants request reconsideration and withdrawal of the rejections for alleged new matter.

Claims 18-20 and 24-25 were rejected under 35 USC § 112, first paragraph as allegedly not enabled. Applicants traverse on the grounds that, in view of the well-developed state of the prior art regarding organ transplantation, the guidance in the specification regarding administration of NO and CO, the level of skill in the transplant field, and what was known in the art regarding inhaled CO, a person of ordinary skill in the art would be able to carry out the claimed methods without undue experimentation.

The examples in the specification demonstrate, in *in vitro* and *in vivo* models of inflammation, the interrelationship between CO/HO-1 and NO/iNOS. Both CO and NO can affect the viability of cells in response to the inflammatory cytokine TNF-α, and HO-1 is required for the effects of both compounds (Figs. 5-6). Similarly, HO-1/CO is required for NO to exert an inhibitory effect on markers of liver injury induced by TNF-α (Fig. 3). These results demonstrate a functional relationship between CO/HO-1 and NO/iNOS.

The Office action states, at page 3, that "[t]he claims encompass the transplantation of any organ with the treatment of the donor with CO and NO." To clarify the record, applicants point out that the sole independent claim under examination (claim 18) is drawn to treatment of the recipient, not the donor. Though this claim does not exclude treatment of the donor as well, it does not require it. (Claims 19, 35 and 36 depend from claim 18 and further require administration to the donor as well as the recipient.)

The Office action says that "the state of the prior art regarding the transplantation of an organ such as a whole brain, for example is nonexistent." Applicants are unsure why the Examiner has chosen to focus on brain transplantation in particular. The state of the prior art

regarding whole-brain transplantation (which doubtless is hampered by ethical considerations)[3]
is not especially relevant considering the well-developed state of the prior art concerning
transplantation of other organs, such as kidney, liver, heart, lung, small bowel, and pancreas.
The first successful human kidney transplantation was performed in 1954, and the art of organ
transplantation has continued to develop rapidly in the half century since. See, e.g., Sayegh and
Carpenter, "Transplantation 50 Year Later – Progress, Challenges, and Promises," N. Engl. J.
Med., 351:2761-66, submitted herewith as Exhibit B. The state of the art regarding organ
transplantation has proceeded to the point that organ transplantations are routine, with more than
25,000 transplantations performed in the U.S. in 2003. *Ibid.* Clearly, the state of the prior art
regarding the transplantation of organs was robust at the present application's priority date. The
Examiner has not provided evidence to the contrary.

The Office action states at page 4 that:

> Pharmaceutical therapies are unpredictable for the following reasons: (1)
> therapeutic compositions may be inactivated before producing an effect;
> (2) the therapeutic composition may not reach the target area; (3) other
> functional properties, known or unknown, may make the therapeutic
> composition unsuitable for in vivo therapeutic use. See page 1338, footnote 7
> of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. App. & Inter. 1992).

The relevance of this statement to the currently claimed methods is not instantly apparent. The
footnote of *Ex parte Aggarwal* cited by the Office Action relates to the examiner's reasoning in
the appealed rejection, and was not relied on by the Board in its opinion. Further, the examiner's
reasoning in *Ex parte Aggarwal* dealt with reasons specific to the protein at issue in that case.
The present Office Action has not given any rationale for concluding that those same reasons
would be generally applicable to all pharmaceutical therapies, or even the particular therapeutic
compositions used in the presently claimed methods. Also, the specification describes in great
detail methods of administering NO and CO and monitoring the effects of their administration.
Further, the example demonstrates administration of NO (in the form of an NO donor) or CO to
mice in amounts effective to reduce markers of liver injury induced by TNF-α/D-gal.

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[3] See the article submitted herewith as Exhibit A (BBC News, "Frankenstein fears after head transplant," April 6,
2001, retrieved from http://news.bbc.co.uk/1/hi/health/1263758.stm), which describes experiments by Dr. Robert
White of Case Western Reserve University regarding brain and head transplantation.

Similarly, the relevance of Calabrese et al. (Xenotransplantation 10:488, Abstract, 2003) and Cozzi et al. (Xenotransplantation 10:528, Abstract, 2003) to the enablement of the claimed methods is not apparent. Calabrese et al. and Cozzi et al. were cited by the Office Action as evidence of "unpredictability in the art of administering CO in order to enhance the transplantation of organs." Office Action, page 4. However, both Calabrese et al. and Cozzi et al. deal with treatment of <u>donors</u> with CO in a pig-to-primate transplantation model, whereas the claims under examination all require treatment of the <u>recipient</u>.

The Office Action also states, at page 5, that "there is no evidence in the present application that NO and CO administration together produce synergistic results in an animal model of transplantation." The relevance of this observation is not clear. The pending claims do not recite or require a synergistic effect. Further, nothing in 35 USC § 112, paragraph 1, requires that a claimed combination therapy produce a synergistic effect, or even an additive effect, in order to meet the enablement requirement. All that is required is that a person of skill in the art be able to use the claimed methods to administer NO and a second treatment specified in the claims (e.g., CO) to enhance survival or function of the organ, tissue, or cells after transplantation of the organ, tissue, or cells to the recipient. In fact, it was shown in U.S. Pat. No. 7,238,469 that administering CO gas to an organ recipient enhances survival of a transplanted organ (heart) or cells (islet cells) in the recipient. See U.S. Pat. No. 7,238,469 at columns 24 to 42. Thus, it is clear that CO alone works when administered to the recipient. The Examiner has not explained why she believes that CO would cease to be effective in the transplantation context if it is co-administered with a composition containing NO, in accordance with the present claims. Indeed, a post-filing date study by Raman et al., 2006, "Inhaled carbon monoxide inhibits intimal hyperplasia and provides added benefit with nitric oxide," J. Vasc. Surg. 44:151-158 (submitted with the IDS filed October 2, 2007), showed that NO therapy (via expression of a vector encoding inducible nitric oxide synthase (iNOS)) did not abrogate the beneficial effects of inhaled CO gas in a porcine model of intimal hyperplasia following vascular injury. In fact, the NO therapy was found to enhance the effects of CO. Though that was not a transplantation experiment, it is sufficient to demonstrate that there is no reason to believe that

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NO therapy would somehow render CO therapy ineffective. Thus, the Examiner's fears that the claimed method with both CO and NO would not work, despite evidence of record that CO alone does work, are not warranted.

Applicants submit that, in view of the above, it is clear that a person of ordinary skill in the art would be able to make and use the claimed methods without undue experimentation. Applicants request reconsideration and withdrawal of the rejection for alleged lack of enablement.

Request for Information

The Office action requested that applicants provide a list of "all copending applications that set forth similar subject matter to the present claims," as well as a copy of the copending claims. Applicants' representatives thank Examiner Sandra Saucier for the courtesy of the telephonic interview held on April 21, 2008. Examiner Saucier stated that she no longer wished to receive copies of the claims in the copending cases and clarified that she only required the disclosure of copending applications that are either co-owned or share overlapping inventorship with the instant application and concern related subject matter. Such copending applications that are either co-owned or share overlapping inventorship and concern related subject matter are listed in the following table:

Serial No.	Applicants	Filed	Status
10/053,535	Choi et al.	01/15/2002	Pending
10/367,277	Otterbein et al.	02/13/2003	Allowed
10/371,666	Otterbein et al.	02/21/2003	Pending
10/413,817	Otterbein et al.	04/15/2003	Pending
10/439,632	Otterbein et al.	05/16/2003	Pending
10/455,564	Otterbein et al.	06/05/2003	Pending
10/511,612	Bach et al.	08/05/2005	Pending
10/676,280	Billiar et al.	09/30/2003	Pending

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11/401,722	Bach et al.	04/10/2006	Pending
11/931,645	Otterbein et al.	10/31/2007	Pending
11/932,634	Otterbein et al.	10/31/2007	Pending
12/050,826	Otterbein et al.	03/18/2008	Pending

Several of these applications were listed in Information Disclosure Statements dated October 29, 2004, September 13, 2007, and December 13, 2007. Application Serial No. 10/367,277 has been allowed, and applicants have been notified by the Office that it will issue on April 29, 2008, as Patent No. 7,364,757. Another related patent, U.S. Patent No. 7,238,469, issued on July 3, 2007.

CONCLUSION

Applicants submit that all pending claims are in condition for allowance, which action is requested. Enclosed is a Petition for Three Month Extension of Time. Please apply the charge of $1050 for the required fee to Deposit Account No. 06-1050. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 13681-012001.

Respectfully submitted,

Date: _April 21, 2008_

Ryan S. McQuade, Ph.D.
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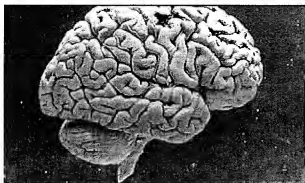Telephone: (617) 542-5070
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EXHIBIT A

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Friday, 6 April, 2001, 10:59 GMT 11:59 UK

Frankenstein fears after head transplant

A new brain could be available in the future

A controversial operation to transplant the whole head of a monkey onto a different body has proved a partial success.

▶ **Professor Robert White**
"We've been able to transplant the brain as a separate organ"
◄» real **28k**

The scientist behind it wants to do the same thing to humans, but other members of the scientific community have condemned the experiments as "grotesque".

Professor Robert White, from Cleveland Ohio, transplanted a whole monkey's head onto another monkey's body, and the animal survived for some time after the operation.

The professor told the BBC's Today programme how he believes the operation is the next step in the transplant world.

And he raised the possibility that it could be used to treat people paralysed and unable to use their limbs, and whose bodies, rather than their brains, were diseased.

"People are dying today who, if they had body transplants, in the spinal injury community would remain alive."

This is medical technology run completely mad

Professor Stephen Rose, Open University

He said that in the experiment, his team had been able to:
"transplant the brain as a separate organ into an intact animal and maintain it in a viable, or

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living situation for many days."

He added: "We've been able to retain the brain in the skull, and in the head."

That, he said meant the monkey was conscious, and that it could see, hear, taste and smell because the nerves were left intact in the head.

He admitted that it could appear "grotesque", but said there had been ethical considerations throughout the history of organ transplants.

"At each stage - kidney, heart, liver and so forth - ethical considerations have been considered, especially with the heart, which was a major, major problem for many people and scientists.

"And the brain, because of its uniqueness poses a major, major ethical issue as far as the public and even the profession is concerned."

'Scientifically misleading'

The arguments against head and brain transplants were outlined by Dr Stephen Rose, director of brain and behavioural research at the Open University.

He said: "This is medical technology run completely mad and out of all proportion to what's needed.

"It's entirely misleading to suggest that a head transplant or a brain transplant is actually really still connected in anything except in terms of blood stream to the body to which it has been transplanted.

"It's not controlling or relating to that body in any other sort of way."

He added: "It's scientifically misleading, technically irrelevant and scientifically irrelevant, and apart from anything else a grotesque breach of any ethical consideration."

"It's a mystification to call it either a head transplant or a brain transplant.

stories are at the foot of the page.

"All you're doing is keeping a severed head alive in terms of the circulation from another animal. It's not connected in any nervous sense."

The issue of who someone who had received a head transplant would "be" is extremely complicated, said Professor Rose.

"Your person is largely embodied but not entirely in your brain".

He added: "I cannot see any medical grounds for doing this. I cannot see that scientifically you would actually be able to regenerate the nerves which could produce that sort of control.

"And I think that the experiments are the sort that are wholly unethical and inappropriate for any possible reason."

He added that the way to help the quadriplegic community was to work on research to help spinal nerves regenerate.

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OCCASIONAL NOTES

Transplantation 50 Years Later —
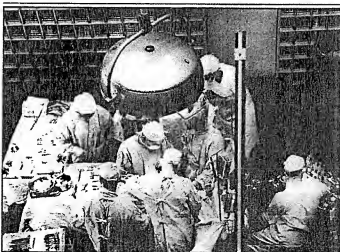# Progress, Challenges, and Promises

Mohamed H. Sayegh, M.D. and Charles B. Carpenter, M.D.

HISTORICAL PERSPECTIVE

On December 23, 1954, a surgical team at the Peter Bent Brigham Hospital in Boston, under the direction of Joseph Murray, removed a kidney from a healthy donor and transplanted it into his identical twin, who had chronic glomerulonephritis and was being sustained on the newly modified Kolff–Brigham artificial kidney machine.[1] The organ functioned immediately,[2] and the recipient survived for nine years, at which time his allograft failed from recurrent glomerulonephritis. The donor has survived for 50 years. Other historical details are provided by Morris elsewhere in this issue of the *Journal*.[3] This first organ transplantation was not an isolated event but, rather, the result of a defined goal of developing a transplantation research program, initiated in the mid-1940s by George W. Thorn, the chairman of medicine, and Francis D. Moore, the chairman of surgery, at Peter Bent Brigham.

As more transplantations were performed between identical twins,[4] approaches to suppressing the recipient's immune system were pursued so that transplantation might be extended beyond procedures involving identical twins. Although the knowledge base in immunology was still rudimentary, the antibodies specific to pathogenic bacteria were well known. Furthermore, in 1925, Emile Holman, a surgeon at Peter Bent Brigham who performed skin grafts in children with extensive burns, reported in 1924 that repeated grafts from maternal donors were rejected more rapidly than the initial grafts, which indicated donor-specific sensitization to the "proteins" of individual volunteer donors.[5] The first approach to suppressing the rejection process, taken in the early 1950s, involved the use of sublethal total-body irradiation combined with cortisone. These attempts were failures, with the exception of some transplantations between nonidentical twins — first at Peter Bent Brigham[6] and a few weeks later in Paris[7] — which provided the impetus to search for more effective ways to prevent rejection.

Robert Schwartz and William Dameshek, hematologists at Tufts University School of Medicine, expanded this horizon in 1959, when they reported that 6-mercaptopurine (6-MP), which was already in clinical use for the treatment of acute lymphocytic leukemia, suppressed the immune response in rabbits.[8,9] The Wellcome Research Laboratory then synthesized several variants of 6-MP for screening by Joseph Murray and Roy Calne in canine kidney transplantations. Only one candidate drug, azathioprine, resulted in long-term survival — and in only a small number of animals. These observations prompted a rather anxious start to the first clinical trial, in 1962, of chemical immunosuppression involving azathioprine.[10] In patients in whom azathioprine was combined with a corticosteroid, one-year rates of allograft survival in the range of 40 to 50 percent were observed, an enormous improvement over the canine results. These clinical breakthroughs were ultimately recognized by awarding of Nobel Prizes to Joseph Murray (and others), for the first

The First Identical-Twin Kidney Transplantation, Performed on December 23, 1954.

Photograph courtesy of Brigham and Women's Hospital.

clinical transplantation and the first use of immunosuppression, and to George Hitchings and Gertrude Elion of the Wellcome Laboratory, for the development of drugs, including azathioprine, that affect nucleotide pathways.

PROGRESS AND CHALLENGES

The rate of successful transplantation of kidneys from cadaveric donors and familial HLA-matched living donors slowly increased during the 1960s and early 1970s, following the introduction of azathioprine with corticosteroids. Although the initial effect was beneficial, prolonged use of corticosteroids resulted in a high mortality rate due to excessive immunosuppression. Overall mortality rates also fell as programs for long-term dialysis improved, which made it possible to discontinue immunosuppression and sustain life when grafts failed. In the early 1980s, cyclosporine was introduced, which increased the rate of one-year graft survival from 70 percent to more than 80 percent.[11] Further developments in the 1980s established the clinical utility of liver, heart, and lung transplantation. More recently, improvement in pancreatic transplantation and early promise in the transplantation of isolated islets have opened up new options for patients with type 1 diabetes.[12-14]

At the end of 2002, in the United States there were 150,000 people living with functioning solid-organ allografts, up from 62,000 in 1993.[15] Trans-plantation has had a worldwide effect; there is significant organ-transplant activity in a large number of other countries.

CHRONIC ALLOGRAFT DYSFUNCTION

During the past decade, as increasing numbers of more powerful immunosuppressive agents became available, the short-term (i.e., 1-year) rate of organ survival significantly improved, yet the long-term results (5-to-10-year survival) did not. Table 1 shows the rates of allograft and patient survival in the United States among patients who received transplants between 1993 and 2002.[16] Table 2 provides the numbers of transplantations for each organ in relation to the size of the waiting lists for those organs.[17]

As Table 1 shows, the survival rates for kidney grafts from living donors are superior to those for grafts from cadaveric donors at 1, 5, and 10 years, but after a decade, the rate drops to 55 percent. Transplants from HLA-identical living donors would be expected to have a survival rate of 70 to 75 percent at 10 years. The initial excitement that followed a report that long-term survival of renal allografts may be improving, especially in recipients who had never had an episode of acute rejection,[18] has faded as newer data[19] showed that, although the rates of acute rejection are at their lowest, the long-term risk of graft loss has not improved and may have even worsened. The reasons for chronic allograft dysfunction involve many factors that concern variable tissue injuries at the time of transplantation or during subsequent episodes of rejection. However, even in the case of grafts with good function in the early years after transplantation, progressive tissue damage and slow decrements in function — conservatively called "chronic allograft dysfunction" — may develop, most often with considerable vasculopathy.[20] Accumulating evidence in animals and humans suggests that there is a consistent pattern in which low-level IgG alloantibodies are directed at HLA antigens, or in which T cells are primed to donor HLA peptides, in those organ-transplant recipients in whom progressive allograft dysfunction occurs.[20-24] Chronic allograft dysfunction affects all transplanted organs and is the most common cause of graft loss after the first year after transplantation.[20]

When a transplanted kidney is rejected, the patient returns to dialysis while waiting for another transplant. The situation with liver transplants differs in that recurrent disease, such as hepatitis C,

remains the
graft loss.[25]
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Table 1. Mean Rates of Graft and Patient Survival for Transplantations in the United States from 1993 through 2002.						
Organ	Survival					
	1 Yr		5 Yr		10 Yr	
	% of grafts	% of patients	% of grafts	% of patients	% of grafts	% of patients
Kidney						
Cadaveric donor	88.7	94.2	65.7	80.7	36.4	57.9
Living donor	94.3	97.5	78.6	90.1	55.2	77.4
Pancreas*						
Alone	77.3	98.6	41.0	79.2	20.5	68.0
With kidney	85.1	94.7	69.8	84.0	46.6	62.7
Liver†	80.6	86.3	64.1	72.1	45.5	55.9
Heart*	85.3	85.6	70.6	72.0	45.6	48.8
Lung†	77.0	78.1	43.6	45.1	18.6	21.9

* These transplants were from cadaveric donors.
† Most of these transplants were from cadaveric donors.

Table 2. Tran
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† In 1993, the

remains the most common cause of long-term graft loss.[25] Since initially high levels of immunosuppression cannot be tolerated over the long term and must be tapered, it is not surprising that breakthroughs in antigen recognition and alloimmune activation can occur. A common feature of drugs used in transplantation,[26] such as DNA-synthesis inhibitors, calcineurin inhibitors, and sirolimus, is their suppression of primary immune responses in naive lymphocytes; these drugs have less of an effect on the expanded clones of primed effector and memory cells.[27] The in vitro culturing of lymphocytes from the peripheral blood with donor HLA peptides that are bound to the antigen-presenting cells of the recipient is a test used to identify the priming of T cells to specific HLA antigens.[28,29] This test is indicative of immunization through the physiologic pathway of T-cell recognition (the "indirect pathway") (Fig. 1), which leads to a switch from IgM to IgG antibodies.[28,30] The "direct pathway," the main driving force in acute rejection, is an anomaly unique to transplantation in which T cells recognize intact HLA molecules on donor cells.[28,29]

In support of the concept that the alloimmune response plays a major role in chronic rejection is the observation that chronic rejection in recipients of kidney transplants is more common in those who have acute rejection and in those who have received HLA-mismatched grafts.[20] In addition, subclinical rejection, as detected by biopsy, without evidence of allograft dysfunction, may be an important contributor to chronic allograft damage.[31] Nonetheless, factors independent of antigens, including fibrosis that is mediated by calcineurin inhibitors,[31] do contribute to chronic graft injury (Fig. 1). The identification of an effective means of preventing or intervening in chronic rejection at an early stage by targeting the factors that are both dependent and independent of alloantigens remains a challenge.[20]

LONG-TERM NEED FOR IMMUNOSUPPRESSION

Immunosuppressive drugs that have been introduced since 1995 have led to combination therapies that have significantly lowered the rates of acute rejection.[19] Induction therapies with various antilymphocyte antibodies also reduce the rate and intensity of acute rejection and possibly prevent the onset of chronic rejection.[26,32] All immunosuppressive drugs have specific side effects and additively contribute to an overall state of immunosuppression, which leads to an increased risk of infections

Table 2. Transplantation According to Organ and Donor Type, 1993 through 2003.

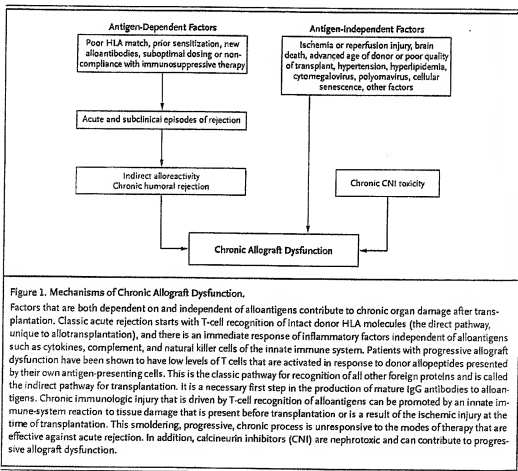| Organ	1993			2003		
	no. of recipients	no. of patients on waiting lists	% receiving transplants	no. of recipients	no. of patients on waiting lists	% receiving transplants
Total						
Cadaveric donor	14,634			18,649		
Living donor	2,898			6,799		
Kidney						
Cadaveric donor	7,444	24,704	30	9,532	56,621	17
Living donor	2,851			6,464		
Pancreas*	758	1,086	70	1,372	4,766	29
Liver						
Cadaveric donor	3,331†	2,931	114	5,349	17,171	31
Living donor	36			320		
Heart*	2,278	2,816	81	2,055	3,519	58
Lung						
Cadaveric donor	660	1,237	53	1,070	3,836	28
Living donor	7			15		

* These transplants were from cadaveric donors.
† In 1993, the supply of livers exceeded the demand, in marked contrast to 2003.

and various specific malignant conditions.[26] Such drugs probably contribute to the increased risk of cardiovascular disease, which is the most common cause of premature death in transplant recipients.[33,34] Excessive immunosuppression causes a susceptibility to infectious diseases,[35] especially to DNA viruses such as cytomegalovirus, Epstein–Barr virus, and the more recently recognized polyomavirus, which causes nephropathy and renal allograft loss.[36]

Over the past two decades, empirical trials have led to protocols of combination therapy that reduce side effects yet maintain graft survival. A major challenge in regard to long-term immunosuppression is the need for expanded multicenter trials of various combination therapies and for the development of inexpensive and noninvasive tools to define and monitor responses along the spectrum of immunity toward, ultimately, tolerance.[37] New candidates for treatment such as T-cell–depleting agents[38-40] and

T-cell blockade,[28,41] all of which are used to modify the immune responses, are under study, and some transplant biologists believe that combinations of drugs without side effects will eventually be available. For example, the use of target-of-rapamycin inhibitors as a way to avoid the use of calcineurin inhibitors in recipients of kidney transplants has recently been reported to improve long-term renal function,[42] decreasing the pathologic changes of chronic allograft nephropathy.[43]

Although a small number of grafts are not rejected after the removal of all or most of the medications used for the maintenance of immunosuppression, trials involving the deliberate withdrawal of immunosuppressive drugs according to protocol do not suggest that it is safe to do so for most patients. One reason is the lack of specific and sensitive assays that can predict the safety of drug withdrawal.[44] Processes of both acute and chronic rejection can occur when therapeutic agents are re-

Figure 1. Mechanisms of Chronic Allograft Dysfunction.

Factors that are both dependent on and independent of alloantigens contribute to chronic organ damage after transplantation. Classic acute rejection starts with T-cell recognition of intact donor HLA molecules (the direct pathway, unique to allotransplantation), and there is an immediate response of inflammatory factors independent of alloantigens such as cytokines, complement, and natural killer cells of the innate immune system. Patients with progressive allograft dysfunction have been shown to have low levels of T cells that are activated in response to donor allopeptides presented by their own antigen-presenting cells. This is the classic pathway for recognition of all other foreign proteins and is called the indirect pathway for transplantation. It is a necessary first step in the production of mature IgG antibodies to alloantigens. Chronic immunologic injury that is driven by T-cell recognition of alloantigens can be promoted by an innate immune-system reaction to tissue damage that is present before transplantation or is a result of the ischemic injury at the time of transplantation. This smoldering, progressive, chronic process is unresponsive to the modes of therapy that are effective against acute rejection. In addition, calcineurin inhibitors (CNI) are nephrotoxic and can contribute to progressive allograft dysfunction.

duced. Nonetheless, the induction of immunologic tolerance by intensive manipulation of recipient immunity during the very early weeks after transplantation remains the ultimate goal.[44] In that regard, the National Institutes of Health Immune Tolerance Network (www.immunetolerance.org) has recently approved various pilot clinical trials designed to explore the biology of tolerance in humans; these studies should shed light on whether such a goal can be achieved.[44,45]

MEDICAL COMPLICATIONS

Whereas infections are responsible for 11.7 percent of deaths in the recipients of primary renal transplants beyond the first year after transplantation, and malignant conditions account for 10.1 percent of such deaths, cardiovascular diseases account for 30.1 percent.[46] Renal dysfunction itself is a cardiovascular risk factor before transplantation, given its association with hypertension, anemia, and lipid disorders.[33] Indeed, renal function one year after transplantation is an important predictor of long-term graft survival in kidney transplantation.[47] Furthermore, renal dysfunction (i.e., dysfunction of native kidneys) is being recognized as a significant clinical problem in recipients of nonrenal solid-organ allografts.[48] Diabetes, which is present in 20 percent of patients who receive transplants,[49] is also an important clinical problem that contributes to the risk of cardiovascular disease and hypertension. In addition, the use of calcineurin inhibitors and corticosteroids is associated with new cases of diabetes after transplantation, and the incidence has been rising in recent years.[50]

ORGAN SHORTAGE

There is a shortage of available organs for patients on waiting lists, and the gap between supply and demand continues to grow[51,52] (Table 2). The consent rate for cadaveric donors is only 50 percent. The increased willingness of living donors other than immediate family members to donate has recently led to some increase in the supply of kidneys.[53] This has also allowed more patients to benefit from preemptive transplantation, which occurs before the institution of long-term dialysis,[54] and thus avoids a period of potential complications. Live-donor laparoscopic nephrectomy, with its shorter recovery time, has helped to increase the willingness to donate. In addition, the use of kidneys from marginal donors — those older than 60 years of age, who were heretofore not accepted as donors because their kidneys are generally unlikely to function for more than five to eight years — is being considered. There are potential opportunities for the exchange of donors in pairs in cases in which there are incompatibilities in the blood group or HLA antibody pattern between an individual donor and recipient. Annual mortality rates among patients on waiting lists for organs from cadaveric donors are currently 6 percent for patients waiting for a kidney, 10 percent for those awaiting a liver, 12 percent for those waiting for a lung, and 14 percent for those who need a heart.[55]

SUMMARY

A half-century has elapsed since the first organ transplantation, and this procedure is now accepted as the treatment of choice for end-stage organ failure. Although tremendous progress has contributed to the success of this therapy, several challenges remain if transplantation is to be widely available with minimal risks and optimal outcomes. Recent advances in the science of organ and cell transplantation provide hope that a variety of chronic diseases will ultimately be cured.

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